Title: Role of oxidative damage in radiation-induced bone loss

Authors: Ann-Sofie Schreurs[1], Joshua S. Alwood[1], Charles L. Limoli[2] and Ruth K. Globus[1]

Affiliation:

[1]NASA Ames Research Center, Space Biosciences Division, Moffett Field, CA 94035, USA

[2]Department of Radiation Oncology, University of California Irvine, Irvine, CA 92697, USA

Abstract:

During prolonged spaceflight, astronauts are exposed to both microgravity and space radiation, and are at risk for increased skeletal fragility due to bone loss. Evidence from rodent experiments demonstrates that both microgravity and ionizing radiation can cause bone loss due to increased bone-resorbing osteoclasts and decreased bone-forming osteoblasts, although the underlying molecular mechanisms for these changes are not fully understood. We hypothesized that excess reactive oxidative species (ROS), produced by conditions that simulate spaceflight, alter the tight balance between osteoclast and osteoblast activities, leading to accelerated skeletal remodeling and culminating in bone loss. To test this, we used the MCAT mouse model; these transgenic mice over-express the human catalase gene targeted to mitochondria, the major organelle contributing free radicals. Catalase is an anti-oxidant that converts reactive species, hydrogen peroxide into water and oxygen. This animal model was selected as it displays extended lifespan, reduced cardiovascular disease and reduced central nervous system radiosensitivity, consistent with elevated anti-oxidant activity conferred by the transgene. We reasoned that mice overexpressing catalase in mitochondria of osteoblast and osteoclast lineage cells would be protected from the bone loss caused by simulated spaceflight. Over-expression of human catalase localized to mitochondria caused various skeletal phenotypic changes compared to WT mice; this includes greater bone length, decreased cortical bone area and moment of inertia, and indications of altered microarchitecture. These findings indicate mitochondrial ROS are important for normal

boneremodeling and skeletal integrity. Catalase over-expression did not fully protect skeletal tissue from structural decrements caused by simulated spaceflight; however there was significant protection in terms of cellular oxidative damage (MDA levels) to the skeletal tissue. Furthermore, we used an array of countermeasures (Antioxidant diets and injections) to prevent the radiation-induced bone loss, although these did not prevent bone loss, analysis is ongoing to determine if these countermeasure protected radiation-induced damage to other tissues.